

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2005/000768

International filing date (day/month/year)
01.03.2005

Priority date (day/month/year)
01.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, C07D519/00, A61K31/5517, A61P35/00

Applicant
SPIROGEN LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/000768

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 24

because:

- ☒ the said international application, or the said claims Nos. 24 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10,25-35
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-35
Industrial applicability (IA)	Yes: Claims	1-23, 25-35
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 11 encompasses many known compounds that it was not possible to cite all documents relevant to the issue of novelty. Therefore only some exemplary documents have been cited.

Claim 24 relates to subject matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

- D1: CHEN ET AL: "A novel approach to the synthesis of cytotoxic C2?C3 unsaturated pyrrolo[2,1-c][and]benzodiazepines (PBDs) with conjugated acrylyl C2-substituents" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 6, 27 February 2004 (2004-02-27), pages 1547-1550, XP002329273
- D2: KANG ET AL: "Synthesis of a novel C2-aryl substituted 1,2-unsaturated pyrrolobenzodiazepine" CHEMICAL COMMUNICATIONS, vol. 14, 11 June 2003 (2003-06-11), pages 1688-1689, XP002329274
- D3: GREGSON ET AL: "Synthesis of the first examples of A-C8/C-C2 amide-Linked pyrrolo[2,1-c][1,4]benzodiazepine dimers" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 13, no. 14, 31 March 2003 (2003-03-31), pages 2277-2280, XP002329063
- D4: COOPER ET AL: "Synthesis of novel C2-aryl pyrrolobenzodiazepines (PBDs) as potential antitumour agents" CHEMICAL COMMUNICATIONS, vol. 16, 5 July 2002

(2002-07-05), pages 1764-1765, XP002329275

- D5: GREGSON ET AL: "Synthesis of the first example of a c2-C3/C2?-C3?-endo unsaturated pyrrolo[2,1-c][1,4]benzodiazepine dimer" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 21, 27 August 2001 (2001-08-27), pages 2859-2862, XP002329276
- D6: GREGSON ET AL: "Effect of C2/C3-endo unsaturation on the cytotoxicity and dna-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 10, no. 16, 14 April 2000 (2000-04-14), pages 1849-1852, XP004216014
- D7: WO 00/12508 A (THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION (GB)) 9 March 2000 (2000-03-09)
- D8: FUKUYAMA ET AL: "Total synthesis of (+)-porothramycin B" TETRAHEDRON LETTERS, vol. 34, no. 16, 16 April 1993 (1993-04-16), pages 2577-2580, XP002135999

Novelty (Article 33(2) PCT)

D1 to D8 disclose compounds with the scope of claim 11. The matter of claims 11 to 24 is therefore not novel.

The compounds of claim 1 differ from the compounds in D1 in the oxygen protecting group R11. Claims 1-10 and 25-35 are therefore novel.

Inventive Step (Article 33(3) PCT)

The problem of claims 1-10 and 25-35 was the provision of a new process and new intermediates for the preparation of compounds of claim 11. D1 could be regarded as the closest prior art.

The present process of claim 31 and the present intermediates of claim 1 are analogous to

the process and intermediates which have already been disclosed in D1. The present intermediates differ only in the use of an oxygen-protecting group R11. The use of oxygen-protecting groups is an obvious measure for a person skilled in the art.

Therefore the present claims 1-10 and 25-35 lack an inventive step.

The problem of claims 11-24 was the provision of new compounds for the treatment of proliferative diseases. D1 could be regarded as the closest prior art. Since the compounds as well as their pharmacology are well known from D1-D8, the matter of claims 11-24 also lacks an inventive step.

Re Item VI

Certain documents cited

Reference is made to the following P-documents:

D9: WO 2004/043963 A (SPIROGEN (GB)) 27 May 2004 (2004-05-27)

D10: TIBERGHIE ET AL: "Application of the Stille coupling reaction to the synthesis of C2-substituted endo-exo unsaturated pyrrolo[2,1-c][1,4]benzodiazepines (PBDs)" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 14, no. 20, 1 September 2004 (2004-09-01), pages 5041-5044, XP002329277

The priority documents pertaining to the present application were not available at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, D9 and D10 could become relevant to assess whether the present claims satisfy the criteria set forth in Article 33(1) PCT.